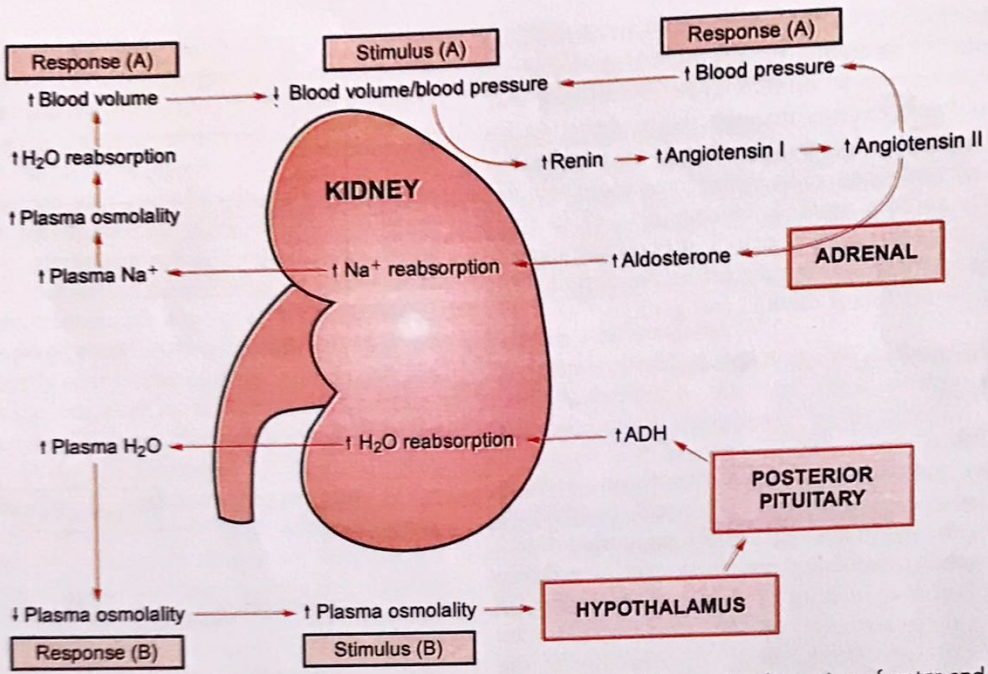

FIGURE 27-4 Antidiuretic hormone (ADH) and aldosterone control of the renal reabsorption of water and Na^+. (Reprinted with permission from Kaplan A, et al. The kidney and tests of renal function. In: Kaplan A, Jack R, Orpheum KE, et al., eds. *Clinical Chemistry: Interpretation and Techniques*. 4th ed. Baltimore, MD: Williams & Wilkins; 1995:158, Figure 6.2.).

Collecting Duct

The collecting ducts are the final site for either concentrating or diluting urine. The hormones ADH and aldosterone act on this segment of the nephron to control reabsorption of water and sodium. Chloride and urea are also reabsorbed here. Urea plays an important role in maintaining the hyperosmolality of the renal medulla. Because the collecting ducts in the medulla are highly permeable to urea, urea diffuses down its concentration gradient out of the tubule and into the medulla interstitium, increasing its osmolality.[3]

Elimination of Nonprotein Nitrogen Compounds

Nonprotein nitrogen compounds (NPNs) are waste products formed in the body as a result of the degradative metabolism of nucleic acids, amino acids, and proteins. Excretion of these compounds is an important function of the kidneys. The three principal compounds are urea, creatinine, and uric acid.[4,5] For a more detailed treatment of their biochemistry and disease correlations, see Chapter 12.

Urea

Urea makes up the majority (more than 75%) of the NPN waste excreted daily as a result of the oxidative catabolism of protein. Urea synthesis occurs in the liver. Proteins are broken down into amino acids, which are then deaminated to form ammonia. Ammonia is readily converted to urea, avoiding toxicity. The kidney is the only significant route of excretion for urea. It has a molecular weight of 60 Da and, therefore, is readily filtered by the glomerulus. In the collecting ducts, 40% to 60% of urea is reabsorbed. The reabsorbed urea contributes to the high osmolality in the medulla, which is one of the processes of urinary concentration mentioned earlier (see loop of Henle).

Creatinine

Muscle contains creatine phosphate, a high-energy compound for the rapid formation of adenosine triphosphate (ATP). This reaction is catalyzed by creatine kinase (CK) and is the first source of metabolic fuel used in muscle contraction. Every day, up to 20% of total muscle creatine (and its phosphate) spontaneously dehydrates and cycles to form the waste product creatinine. Therefore, creatinine levels are a function of muscle mass and remain approximately the same in an individual from day-to-day unless muscle mass or renal function changes. Creatinine has a molecular weight of 113 Da and is, therefore, readily filtered by the glomerulus. Unlike urea, creatinine is not reabsorbed by the tubules. However, a small amount of creatinine is secreted by the kidney tubules at high serum concentrations.

Uric Acid

Uric acid is the primary waste product of purine metabolism. The purines, adenine and guanine, are precursors of nucleic acids ATP and guanosine triphosphate,

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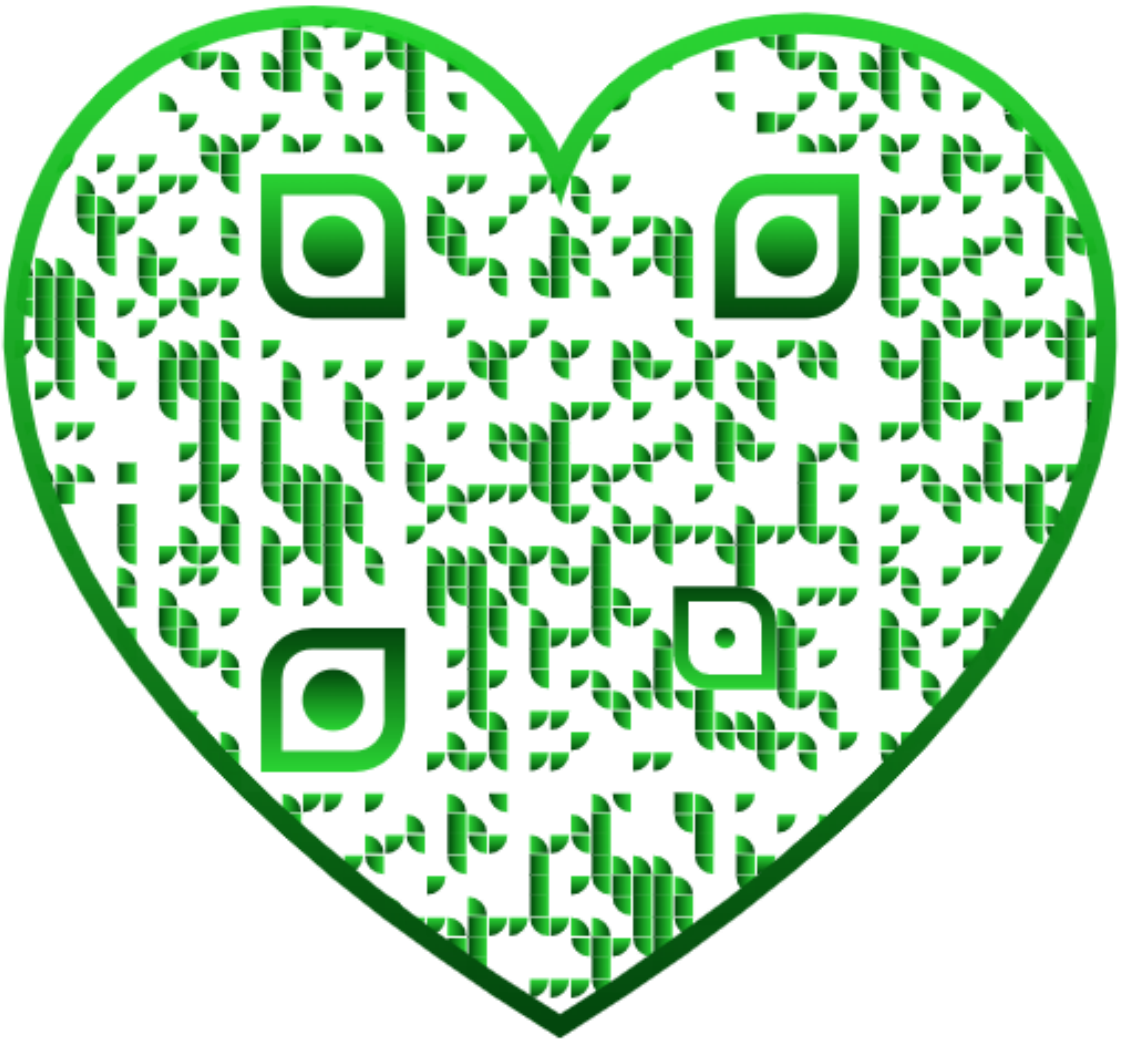

respectively. Uric acid has a molecular weight of 168 Da. Like creatinine, it is readily filtered by the glomerulus, but it then undergoes a complex cycle of reabsorption and secretion as it courses through the nephron. Only 6% to 12% of the original filtered uric acid is finally excreted. Uric acid exists in its ionized and more soluble form, usually sodium urate, at urinary pH > 5.75 (the first pK_a of uric acid). At pH < 5.75, it is undissociated. This fact has clinical significance in the development of urolithiasis (formation of calculi) and gout.

Water, Electrolyte, and Acid–Base Homeostasis

Water Balance

The kidney's contribution to water balance in the body is through water loss or water conservation, which is regulated by the hormone ADH. ADH responds primarily to changes in osmolality and intravascular volume. Increased plasma osmolality or decreased intravascular volume stimulates secretion of ADH from the posterior pituitary. ADH then increases the permeability of the distal convoluted tubules and collecting ducts to water, resulting in increased water reabsorption and excretion of more concentrated urine. In contrast, the major system regulating water intake is thirst, which appears to be triggered by the same stimuli that trigger ADH secretion.

In states of dehydration, the renal tubules reabsorb water at their maximal rate, resulting in production of a small amount of maximally concentrated urine (high urine osmolality, 1,200 mOsm/L).[6] In states of water excess, the tubules reabsorb water at only a minimal rate, resulting in excretion of a large volume of extremely dilute urine (low urine osmolality, down to 50 mOsm/L).[7,8] The continuous fine-tuning possible between these two extreme states results in the precise control of fluid balance in the body (Fig. 27-5).

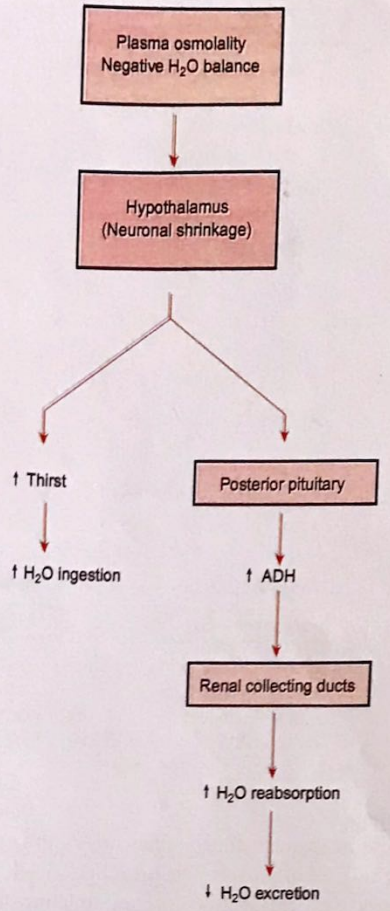

FIGURE 27-5 Antidiuretic hormone (ADH) control of thirst mechanism.

Electrolyte Balance

The following is a brief overview of the notable ions involved in maintenance of electrolyte balance within the body. For a more comprehensive treatment of this subject, refer Chapter 16.

Sodium

Sodium is the primary extracellular cation in the human body and is excreted principally through the kidneys. Sodium balance in the body is controlled only through excretion. The renin–angiotensin–aldosterone hormonal system is the major mechanism for the control of sodium balance.

Potassium

Potassium is the main intracellular cation in the body. The precise regulation of its concentration is of extreme importance to cellular metabolism and is controlled chiefly by renal means. Like sodium, it is freely filtered by the glomerulus and then actively reabsorbed throughout the entire nephron (except for the descending limb of the loop of Henle). Both the distal convoluted tubule and the collecting ducts can reabsorb and excrete potassium, and this excretion is controlled by aldosterone. Potassium ions can compete with hydrogen ions in their exchange with sodium (in the proximal convoluted tubule); this process is used by the body to conserve hydrogen ions and, thereby, compensate in states of metabolic alkalosis.

Chloride

Chloride is the principal extracellular anion and is involved in the maintenance of extracellular fluid balance. It is readily filtered by the glomerulus and is passively reabsorbed as a counterion when sodium is reabsorbed in the proximal convoluted tubule. In the ascending limb of the loop of Henle, potassium is actively reabsorbed by a distinct chloride "pump," which also reabsorbs sodium. This pump can be inhibited by loop diuretics, such as furosemide. As expected, the regulation of chloride is controlled by the same forces that regulate sodium.[6,8]

Phosphate, Calcium, and Magnesium

The phosphate ion occurs in higher concentrations in the intracellular than in the extracellular fluid environments. It exists as either a protein-bound or a non–protein-bound form; homeostatic balance is chiefly determined by proximal tubular reabsorption under the control of parathyroid hormone (PTH). Calcium, the second-most predominant intracellular cation, is the most important inorganic messenger in the cell. It also exists in protein-bound and non–protein-bound states. Calcium in the non–protein-bound form is either ionized and physiologically active or nonionized and complexed to small, diffusible ions, such as phosphate and bicarbonate. The ionized form is freely filtered by the glomerulus and reabsorbed in the tubules under the control of PTH. However, renal control of calcium concentration is not the major means of regulation. PTH- and calcitonin-controlled regulation of calcium absorption from the gut and bone stores is more important than renal secretion or reabsorption. Magnesium, a major intracellular cation, is important as an enzymatic cofactor. Like phosphate and calcium, it exists in both protein-bound and ionized states. The ionized fraction is easily filtered by the glomerulus and reabsorbed in the tubules under the influence of PTH. See Chapter 24 for more detailed information.

Acid–Base Balance

Many nonvolatile acidic waste products are formed by normal body metabolism each day. Carbonic acid, lactic acid, ketoacids, and others must be continually transported in the plasma and excreted from the body, causing only minor alterations in physiologic pH. The renal system constitutes one of three means by which constant control of overall body pH is accomplished. The other two strategies involved in this regulation are the respiratory system and the acid–base buffering system.[9]

The kidneys manage their share of the responsibility for controlling body pH by dual means: conserving bicarbonate ions and removing metabolic acids. For a more in-depth examination of these processes, refer Chapter 17.

Regeneration of Bicarbonate Ions

In a complicated process, bicarbonate ions are first filtered out of the plasma by the glomerulus. In the lumen of the renal tubules, this bicarbonate combines with hydrogen ions to form carbonic acid, which subsequently degrades to carbon dioxide (CO_2) and water. This CO_2 then diffuses into the brush border of the proximal tubular cells, where it is reconverted by carbonic anhydrase to carbonic acid and then degrades back to hydrogen ions and regenerated bicarbonate ions. This regenerated bicarbonate is transported into the blood to replace what was depleted by metabolism; the accompanying hydrogen ions are secreted back into the tubular lumen, and from there, they enter the urine. Filtered bicarbonate is "reabsorbed" into the circulation, helping to return blood pH to its optimal level and effectively functioning as another buffering system.

Excretion of Metabolic Acids

Hydrogen ions are manufactured in the renal tubules as part of the regeneration mechanism for bicarbonate. These hydrogen ions, as well as others that are dissociated from nonvolatile organic acids, are disposed of by several different reactions with buffer bases.

Reaction with Ammonia (NH_3)

The glomerulus does not filter NH_3. However, this substance is formed in the renal tubules when the amino acid glutamine is deaminated by glutaminase. This NH_3 then reacts with secreted hydrogen ions to form ammonium ions (NH_4^+), which are unable to readily diffuse out of the tubular lumen and, therefore, are excreted into the urine. This mode of acid excretion is the primary means by which the kidneys compensate for states of metabolic acidosis.

Reaction with Monohydrogen Phosphate (HPO_4^{-2})

Phosphate ions filtered by the glomerulus can exist in the tubular fluid as disodium hydrogen phosphate (Na_2HPO_4) (dibasic). This compound can react with hydrogen ions to yield dihydrogen phosphate (monobasic), which is then excreted. The released sodium then combines with bicarbonate to yield sodium bicarbonate and is reabsorbed. These mechanisms can excrete increasing amounts of metabolic acid until a maximum urine pH of approximately 4.4 is reached. After this, renal compensation is unable to adjust to any further decreases in blood pH and metabolic acidosis ensues. Few free hydrogen ions are excreted directly in the urine.

Endocrine Function

In addition to numerous excretory and regulatory functions, the kidney has endocrine functions as well. It is both a primary endocrine site, as the producer of its own hormones, and a secondary site, as the target locus for hormones manufactured by other endocrine organs. The kidneys synthesize renin, erythropoietin, 1,25-dihydroxy vitamin D_3, and the prostaglandins.

Renin

Renin is the initial component of the renin–angiotensin–aldosterone system. Renin is produced by the juxtaglomerular cells of the renal medulla when extracellular fluid volume or blood pressure decreases. It catalyzes the synthesis of angiotensin by cleavage of the circulating plasma precursor angiotensinogen. Angiotensin is converted to angiotensin II by angiotensin-converting enzyme. Angiotensin II is a powerful vasoconstrictor that increases blood pressure and stimulates release of aldosterone from the adrenal cortex. Aldosterone, in turn, promotes sodium reabsorption and water conservation.[7,8]

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For a more detailed look at the complexities of this feedback loop, see Chapter 21.

Erythropoietin

Erythropoietin is a single-chain polypeptide produced by cells close to the proximal tubules, and its production is regulated by blood oxygen levels. Hypoxia produces increased serum concentrations within 2 hours. Erythropoietin acts on the erythroid progenitor cells in the bone marrow, increasing the number of red blood cells (RBCs). In chronic renal insufficiency, erythropoietin production is significantly reduced. Recently, recombinant human erythropoietin has been developed and is in routine use in chronic renal failure patients. Before this therapy, anemia was a clinical reality in these patients.[4,7] Erythropoietin concentrations in blood can be measured by immunoassays. Recombinant human erythropoietin has also been used in sports doping to stimulate erythrocyte production and increase the oxygen-carrying capacity in the blood of endurance athletes. Assays capable of detecting post-translational modifications on erythropoietin have been produced and are capable of distinguishing exogenous from endogenous erythropoietin.

1,25-Dihydroxy Vitamin D_3

The kidneys are the sites of formation of the active form of **vitamin D**, 1,25-$(OH)_2$ vitamin D_3. This form of vitamin D is one of three major hormones that determine phosphate and calcium balance and bone calcification in the human body. Chronic renal insufficiency is, therefore, often associated with osteomalacia (inadequate bone calcification, the adult form of rickets), owing to the continual distortion of normal vitamin D metabolism.

Prostaglandins

The prostaglandins are a group of potent cyclic fatty acids formed from essential (dietary) fatty acids, primarily arachidonic acid. They are formed in almost all tissue and their actions are diverse. The prostaglandins produced by the kidneys increase renal blood flow, sodium and water excretion, and renin release. They act to oppose renal vasoconstriction due to angiotensin and norepinephrine.

ANALYTIC PROCEDURES

All laboratory methods used for the evaluation of renal function rely on the measurement of waste products in blood, usually urea and creatinine, which accumulate when the kidneys begin to fail. Renal failure must be advanced, with only about 20% to 30% of the nephrons still functioning, before the concentration of either substance begins to increase in the blood. The rate at which creatinine and urea are removed or cleared from the blood into the urine is termed clearance. Clearance is defined as that volume of plasma from which a measured amount of substance can be completely eliminated into the urine per unit of time expressed in milliliters per minute.[5] Calculation of creatinine clearance has become the standard laboratory method for determining the GFR. Urea clearance was one of the first clearance tests performed; however, it is no longer widely used since it does not accurately provide a full clearance assessment. Older tests used administration of insulin, sodium [^{125}I] iothalamate, or *p*-aminohippurate to assess glomerular filtration or tubular secretion. These tests are difficult to administer and are no longer common.

Creatinine Clearance

Creatinine is a nearly ideal substance for the measurement of clearance. It is an endogenous metabolic product synthesized at a constant rate for a given individual and cleared essentially only by glomerular filtration. It is not reabsorbed and is only slightly secreted by the proximal tubule. Serum creatinine levels are higher in males than in females due to the direct correlation with muscle mass. Analysis of creatinine is simple and inexpensive using colorimetric assays; however, different methods for assaying plasma creatinine, such as kinetic or enzymatic assays, have varying degrees of accuracy and imprecision (see Chapter 12).

Creatinine clearance is derived by mathematically relating the serum creatinine concentration to the urine creatinine concentration excreted during a period of time, usually 24 hours. Specimen collection, therefore, must include both a 24-hour urine specimen and a serum creatinine value, ideally collected at the midpoint of the 24-hour urine collection. The urine container must be kept refrigerated throughout the duration of both the collection procedure and the subsequent storage period until laboratory analysis can be performed. The concentration of creatinine in both serum and urine is measured by the applicable methods discussed in Chapter 12. The total volume of urine is carefully measured, and the creatinine clearance is calculated using the following formula:

$$\frac{U_{Cr}(\text{mg/dL}) \times V_{Ur}(\text{mL/24hours})}{P_{Cr}(\text{mg/dL}) \times 1{,}440 \text{ minutes/24hours}} \times \frac{1.73}{A} \quad \text{(Eq. 27-1)}$$

where Cr is creatinine clearance, U_{Cr} is urine creatinine clearance, V_{Ur} is urine volume excreted in 24 hours, P_{Cr} is serum creatinine concentration, and 1.73/*A* is normalization factor for body surface area (1.73 is the generally accepted average body surface in square meters and *A* is the actual body surface area of the individual determined from height and weight). If the patient's body surface area varies greatly from the average (e.g., obese or pediatric patients), this correction for body mass must be included in the formula. Nomograms for the more exact determination of body surface area from weight and

height values can be found in Appendix E. The reference range for creatinine clearance is lower in females compared with males and normally decreases with age.

Estimated GFR

The National Kidney Foundation recommends that **estimated GFR** (eGFR) be calculated each time a serum creatinine level is reported. (Additional information is available at the National Kidney Foundation web site at http://www.kidney.org/.) The equation is used to predict GFR and is based on serum creatinine, age, body size, gender, and race, without the need of a urine creatinine. Because the calculation does not require a timed urine collection, it should be used more often than the traditional creatinine clearance and result in earlier detection of **chronic kidney disease** (CKD). There are a number of formulas that can be used to estimate GFR on the basis of serum creatinine levels.

Cockcroft-Gault Formula

The Cockcroft-Gault formula is one of the first formulas used to estimate GFR. This formula predicts creatinine clearance and the results are not corrected for body surface area. This equation assumes that women will have a 15% lower creatinine clearance than men at the same level of serum creatinine.

$$\text{GFR (mL/min)} = \frac{(140 - \text{Age}) \times \text{Weight(kg)}}{72 \times S_{Cr}(\text{mg/dL})} \times (0.85 \text{ if female}) \quad \text{(Eq. 27-2)}$$

Modification of Diet in Renal Disease Formula

The modification of diet in renal disease (MDRD) formula was developed in the Modification of Diet in Renal Disease Study of chronic renal insufficiency. The study showed that the MDRD formula provided a more accurate assessment of GFR than the Cockcroft-Gault formula. The MDRD formula was validated in a large population that included European Americans and African Americans. It does not require patient weight and is corrected for body surface area. The MDRD formula is known to underestimate the GFR in healthy patients with GFRs over 60 mL/min and to overestimate GFR in underweight patients. The four-variable MDRD equation includes age, race, gender, and serum creatinine as variables.

$$\text{GFR (mL/min/1.73 m}^2) = 186 \times S_{Cr}(\text{mg/dL})^{-1.154} \times \text{Age}^{-0.203} \times (1.212 \text{ if Black}) \times (0.742 \text{ if female}) \quad \text{(Eq. 27-3)}$$

CKD-EPI Formula

The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula was published in 2009. It was developed in an effort to create a formula more accurate than the MDRD formula. Multiple studies have shown the CKD-EPI formula to perform better and with less bias than the MDRD formula, especially in patients with higher GFR. Most laboratories still use the MDRD formula; however, some have converted to the CKD-EPI formula.

$$\text{eGFR(mL/min/1.73 m}^2) = 141 \times \min(S_{Cr}/k,1)^a \times \max(S_{Cr}/k,1)^{-1.209} \times 0.993^{\text{Age}} \times (1.018 \text{ if female}) \times (1.159 \text{ if Black}) \quad \text{(Eq. 27-4)}$$

k is 0.7 for females and 0.9 for males, a is –0.329 for females and –0.411 for males, min indicates the minimum of S_{Cr}/k or 1, and max indicates the maximum of S_{Cr}/k or 1.

Cystatin C

Cystatin C is a low-molecular-weight protein produced at a steady rate by most body tissues. It is freely filtered by the glomerulus, reabsorbed, and catabolized by the proximal tubule. Levels of cystatin C rise more quickly than creatinine levels in acute renal failure. Plasma concentrations appear to be unaffected by diet, gender, race, age, and muscle mass. Studies have shown measurement of cystatin C to be at least as useful as serum creatinine and creatinine clearance in detecting early changes in kidney function. A rise in cystatin C is often detectable before there is a measureable decrease in the GFR or increase in creatinine. Cystatin C can be measured by immunoassay methods.[11] Recent findings suggest that an equation that uses both serum creatinine and cystatin C with age, sex, and race would be better than equations that use only one of these serum markers.[12,13]

Biologic Variation

When the same test is performed on various individuals, we find that the mean of each person's results is not the same, showing that individual homeostatic setting points often vary. Biologic variation is defined as the random fluctuation around a homeostatic setting point.[14] This includes the fluctuation around the homeostatic setting point for a single individual, termed within-subject biologic variation, and differences between the homeostatic setting points of multiple individuals, termed between-subject biologic variation. In the case of creatinine, levels for an individual differ slightly over time, and the mean values of all individuals vary significantly from each other. Therefore, each individual's results span only a small portion of the population-based reference interval. This means that for creatinine, within-subject biologic variation is less than between-subject biologic variation. When this is true of a given analyte, the analyte is said to have marked individuality. Interestingly, the between-subject biologic variation is much smaller for cystatin C compared with creatinine, showing that population-based reference values are more useful for cystatin C compared with creatinine. However, the within-subject variation is greater for cystatin C compared

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with creatinine. As a result, creatinine is more helpful in monitoring renal function over time for a given individual, whereas cystatin C is potentially more useful for detecting minor renal impairment.

β_2-Microglobulin

β_2-Microglobulin (β2-M) is a small, nonglycosylated peptide (molecular weight, 11,800 Da) found on the surface of most nucleated cells. The plasma membrane sheds β2-M at a constant rate, as a relatively intact molecule. β2-M is easily filtered by the glomerulus and 99.9% is reabsorbed by the proximal tubules and catabolized. Elevated levels in serum indicate increased cellular turnover as seen in myeloproliferative and lymphoproliferative disorders, inflammation, and renal failure. Both blood and urine β2-M tests may be ordered to evaluate kidney damage and to distinguish between disorders that affect the glomeruli and the renal tubules. Measurement of serum β2-M is used clinically to assess renal tubular function in renal transplant patients, with elevated levels indicating organ rejection.

Myoglobin

Myoglobin is a low-molecular-weight protein (16,900 Da) associated with acute skeletal and cardiac muscle injury. Myoglobin functions to bind and transport oxygen from the plasma membrane to the mitochondria in muscle cells. Blood levels of myoglobin can rise very quickly with severe muscle injury. In rhabdomyolysis, myoglobin release from skeletal muscle is sufficient to overload the proximal tubules and cause acute renal failure. Early diagnosis and aggressive treatment of elevated myoglobin may prevent or lessen the severity of renal failure. Serum and urine myoglobin can be measured easily and rapidly by immunoassays.

Microalbumin

The term *microalbuminuria* describes small amounts of albumin in the urine. Urine microalbumin measurement is important in the management of patients with diabetes mellitus, who are at serious risk for developing nephropathy over their lifetime. In the early stages of nephropathy, there is renal hypertrophy, hyperfunction, and increased thickness of the glomerular and tubular basement membranes. In this early stage, there are no overt signs of renal dysfunction. In the next 7 to 10 years, there is progression to glomerulosclerosis, with increased glomerular capillary permeability. This permeability allows small (micro) amounts of albumin to pass into the urine. If detected in this early phase, rigid glucose control, along with treatment to prevent hypertension, can be instituted and progression to kidney failure prevented. Quantitative albumin-specific immunoassays, usually using nephelometry or immunoturbidimetry, are widely used. For a 24-hour urine collection, 30 to 300 mg of albumin is diagnostic of microalbuminuria. A 24-hour urine collection is preferred, but a random urine sample that uses a ratio of albumin to creatinine can also be used. An albumin to creatinine ratio of >30 mg/g is diagnostic of microalbuminuria.

Neutrophil Gelatinase–Associated Lipocalin

Neutrophil gelatinase–associated lipocalin (NGAL) is a 25-kDa protein expressed by neutrophils and epithelial cells including those of the proximal tubule. The gene encoding NGAL is upregulated in the presence of renal ischemia, tubule injury, and nephrotoxicity.[15] It can be measured in plasma and urine and is elevated within 2 to 6 hours of acute kidney injury (AKI). NGAL has been shown to be a useful early predictor of AKI and has prognostic value for clinical endpoints, such as initiation of dialysis and mortality. However, urinary NGAL excretion may also arise from systemic stress in the absence of AKI, limiting its specificity.

Urinalysis

Urinalysis (UA) permits a detailed, in-depth assessment of renal status with an easily obtained specimen. UA also serves as a quick indicator of an individual's glucose status and hepatic–biliary function. Routine UA includes assessment of physical characteristics, chemical analyses, and a microscopic examination of the sediment from a (random) urine specimen.

Specimen Collection

The importance of a properly collected and stored specimen for UA cannot be overemphasized. Initial morning specimens are preferred, particularly for protein analyses, because they are more concentrated from overnight retention in the bladder. The specimen should be obtained by a clean midstream catch or catheterization. The urine should be freshly collected into a clean, dry container with a tight-fitting cover. It must be analyzed within 1 hour of collection if held at room temperature or else refrigerated at 2°C to 8°C for not more than 8 hours before analysis. If not assayed within these time limits, several changes will occur. Bacterial multiplication will cause false-positive nitrite tests, and urease-producing organisms will degrade urea to ammonia and alkalinize the pH. Loss of CO_2 by diffusion into the air adds to this pH elevation, which, in turn, causes cast degeneration and red cell lysis.

Physical Characteristics

Visual Appearance

Color intensity of urine correlates with concentration: the darker the color, the more concentrated is the specimen. The various colors observed in urine are a result of different excreted pigments. Yellow and amber are generally due to urochromes (derivatives of urobilin, the end product of bilirubin degradation), whereas a yellowish-brown

to green color is a result of bile pigment oxidation. Red and brown after standing are due to porphyrins, whereas reddish-brown in fresh specimens comes from hemoglobin or red cells. Brownish-black after standing is seen in alkaptonuria (a result of excreted homogentisic acid) and in malignant melanoma (in which the precursor melanogen oxidizes in the air to melanin). Drugs and some foods, such as beets, may also alter urine color.

Odor

Odor ordinarily has little diagnostic significance. The characteristic pungent odor of fresh urine is due to volatile aromatic acids, in contrast to the typical ammonia odor of urine that has been allowed to stand. Urinary tract infections impart a noxious, fecal smell to urine, whereas the urine of diabetics often smells fruity as a result of ketones. Certain inborn errors of metabolism, such as maple sugar urine disease, are associated with characteristic urine odors.

Turbidity

The cloudiness of an urine specimen depends on pH and dissolved solids composition. Turbidity generally may be due to gross bacteriuria, whereas a smoky appearance is seen in hematuria. Thread-like cloudiness is observed when the specimen is full of mucus. In alkaline urine, suspended precipitates of amorphous phosphates and carbonates may be responsible for turbidity, whereas in acidic urine, amorphous urates may be the cause.[16]

Volume

The volume of urine excreted indicates the balance between fluid ingestion and water lost from the lungs, sweat, and intestine. Most adults produce from 750 to 2,000 mL every 24 hours, averaging about 1.5 L per person. Polyuria is observed in diabetes mellitus and insipidus (in insipidus, as a result of lack of ADH), as well as in chronic renal disease, acromegaly (overproduction of the growth hormone somatostatin), and myxedema (hypothyroid edema). Anuria or oliguria (<200 mL/d) is found in nephritis, urinary tract obstruction, AKI, and kidney failure.

Specific Gravity

The specific gravity (SG) of urine is the weight of 1 mL of urine in grams divided by the weight of 1 mL of water. SG gives an indication of the density of a fluid that depends on the concentration of dissolved total solids. SG varies with the solute load to be excreted (consisting primarily of NaCl and urea), as well as with the urine volume. It is used to assess the state of hydration/dehydration of an individual or as an indicator of the concentrating ability of the kidneys.

The most commonly encountered analytic method consists of a refractometer, or total solids meter. This operates on the principle that the refractive index of a urine specimen will vary directly with the total amount of dissolved solids in the sample. This instrument measures the refractive index of the urine as compared with water on a scale that is calibrated directly into the ocular and viewed while held up to a light source. Correct calibration is vital for accuracy. Most recently, an indirect colorimetric reagent strip method for assaying SG has been added to most dipstick screens. Unlike the refractometer, dipsticks measure only ionic solutes and do not take into account glucose or protein.

The normal range for urinary SG is 1.003 to 1.035 g/mL. SG can vary in pathologic states. Low SG can occur in diabetes insipidus, pyelonephritis, and glomerulonephritis, in which the renal concentrating ability has become dysfunctional. High SG can be seen in diabetes mellitus, congestive heart failure, dehydration, adrenal insufficiency, liver disease, and nephrosis. SG will increase about 0.004 units for every 1% change in glucose concentration and about 0.003 units for every 1% change in protein. Fixed SG (isosthenuria) around 1.010 is observed in severe renal damage, in which the kidney excretes urine that is iso-osmotic with the plasma. This generally occurs after an initial period of anuria because the damaged tubules are unable to concentrate or dilute the glomerular filtrate.[16]

pH

Determinations of urinary pH must be performed on fresh specimens because of the significant tendency of urine to alkalinize on standing. Normal urine pH falls within the range of 4.7 to 7.8. Acidity in urine (pH < 7.0) is primarily caused by phosphates, which are excreted as salts conjugated to Na^+, K^+, Ca^{2+}, and NH_4^+. Acidity also reflects the excretion of the nonvolatile metabolic acids pyruvate, lactate, and citrate. Owing to the Na^+/H^+ exchange pump mechanism of the renal tubules, pH (H^+ concentration) increases as sodium is retained. Pathologic states, in which increased acidity is observed, include systemic acidosis, as seen in diabetes mellitus, and renal tubular acidosis (RTA). In RTA, the tubules are unable to excrete excess H^+ even though the body is in metabolic acidosis, and urinary pH remains around 6.

Alkaline urine (pH > 7.0) is observed postprandially as a normal reaction to the acidity of gastric HCl dumped into the duodenum and then into the circulation or following ingestion of alkaline food or medications. Urinary tract infections and bacterial contamination also will alkalinize pH. Medications such as potassium citrate and sodium bicarbonate will reduce urine pH. Alkaline urine is also found in Fanconi syndrome, a congenital generalized aminoaciduria resulting from defective proximal tubular function.

Chemical Analyses

Routine urine chemical analysis is rapid and easily performed with commercially available reagent strips or dipsticks. These strips are plastic coated with different reagent bands directed toward different analytes. When dipped into urine, a color change signals a deviation from normality. Colors on the dipstick bands are matched against a color chart provided with the reagents. Automated and semiautomated instruments that detect

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by reflectance photometry provide an alternative to the color chart and offer better precision and standardization. Abnormal results are followed up by specific quantitative or confirmatory urine assays. The analytes routinely tested are glucose, protein, ketones, nitrite, leukocyte esterase, bilirubin/urobilinogen, and hemoglobin/blood.

Glucose and Ketones

These constituents are normally absent in urine. The clinical significance of these analytes and their testing methods are discussed in Chapter 14.

Protein

Reagent strips for UA are used as a general qualitative screen for proteinuria. They are primarily specific for albumin, but they may give false-positive results in specimens that are alkaline and highly buffered. Positive dipstick results should be confirmed by more specific chemical assays, as described in Chapter 11, or more commonly by microscopic evaluation to detect casts.

Nitrite

This assay semiquantitates the amount of urinary reduction of nitrate (on the reagent strip pad) to nitrite by the enzymes of gram-negative bacteria. A negative result does not mean that no bacteriuria is present. A gram-positive pathogen, such as *Staphylococcus*, *Enterococcus*, or *Streptococcus*, may not produce nitrate-reducing enzymes; alternatively, a spot urine sample may not have been retained in the bladder long enough to pick up a sufficient number of organisms to register on the reagent strip.[16]

Leukocyte Esterase

White blood cells (WBCs), especially phagocytes, contain esterases. A positive dipstick for esterases indicates possible WBCs in urine.

Bilirubin/Urobilinogen

Hemoglobin degradation ultimately results in the formation of the waste product bilirubin, which is then converted to urobilinogen in the gut through bacterial action. Although most of this urobilinogen is excreted as urobilin in the feces, some is excreted in urine as a colorless waste product. This amount is normally too small to be detected as a positive dipstick reaction. In conditions of prehepatic, hepatic, and posthepatic jaundice, however, urine dipstick tests for urobilinogen and bilirubin may be positive or negative, depending on the nature of the patient's jaundice. A more in-depth view of bilirubin metabolism and assay methods is given in Chapter 25. Reagent strip tests for bilirubin involve diazotization and formation of a color change. Dipstick methods for urobilinogen differ, but most rely on a modification of the Ehrlich reaction with *p*-dimethylaminobenzaldehyde.[16]

Hemoglobin/Blood

Intact or lysed RBCs produce a positive dipstick result. The dipstick will be positive in cases of renal trauma/injury, infection, and obstruction that result from calculi or neoplasms.

Sediment Examination

Centrifuged, decanted urine aliquot leaves behind a sediment of formed elements that is used for microscopic examination.

Cells

For cellular elements, evaluation is best accomplished by counting and then taking the average of at least 10 microscopic fields.

Red Blood Cells

Erythrocytes greater in number than 0 to 2/high-power field (HPF) are considered abnormal. Such hematuria may result simply from severe exercise or menstrual blood contamination. However, it may also be indicative of trauma, particularly vascular injury, renal/urinary calculi obstruction, pyelonephritis, or cystitis. Hematuria in conjunction with leukocytes is diagnostic of infection.

White Blood Cells

Leukocytes greater in number than 0 to 1/HPF are considered abnormal. These cells are usually polymorphonuclear phagocytes, commonly known as segmented neutrophils. They are observed when there is acute glomerulonephritis, urinary tract infection, or inflammation of any type. In hypotonic urine (low osmotic concentration), WBCs can become enlarged, exhibiting a sparkling effect in their cytoplasmic granules. These cells possess a noticeable Brownian motion and are called glitter cells, but they have no pathologic significance.

Epithelial Cells

Several types of epithelial cells are frequently encountered in normal urine because they are continuously sloughed off the lining of the nephrons and urinary tract. Large, flat, squamous vaginal epithelia are often seen in urine specimens from female patients, and samples heavily contaminated with vaginal discharge may show clumps or sheets of these cells. Renal epithelial cells are round, uninucleate cells and, if present in numbers greater than 2/HPF, indicate clinically significant active tubular injury or degeneration. Transitional bladder epithelial cells (urothelial cells) may be flat, cuboidal, or columnar and also can be observed in urine on occasion. Large numbers will be seen only in cases of urinary catheterization, bladder inflammation, or neoplasm.

Miscellaneous Elements

Spermatozoa are often seen in the urine of both males and females. They are usually not reported because they are of no pathologic significance. In males, however, their presence may indicate prostate abnormalities. Yeast cells are also frequently found in urine specimens. Because they are extremely refractile and of a similar size to RBCs, they can easily be mistaken under low magnification. Higher power examination for budding or mycelial forms differentiates these fungal elements from erythrocytes. Parasites found in urine are generally contaminants from fecal or vaginal material. In fecal contaminant category,

the most commonly encountered organism is *Enterobius vermicularis* (pinworm) infestation in children. In the vaginal contaminant category, the most common is the intensely motile flagellate, *Trichomonas vaginalis*. A true urinary parasite, sometimes seen in patients from endemic areas of the world, is the ova of the trematode *Schistosoma haematobium*. This condition will usually occur in conjunction with a significant hematuria.[16]

Bacteria

Normal urine is sterile and contains no bacteria. Small numbers of organisms seen in a fresh urine specimen usually represent skin or air contamination. In fresh specimens, however, large numbers of organisms, or small numbers accompanied by WBCs and the symptoms of urinary tract infection, are highly diagnostic for true infection. Clinically significant bacteriuria is considered to be more than 20 organisms/HPF or, alternatively, 10^5 or greater registered on a microbiologic colony count. Most pathogens seen in urine are gram-negative coliforms (microscopic "rods") such as *Escherichia coli* and *Proteus* spp. Asymptomatic bacteriuria, in which there are significant numbers of bacteria without appreciable clinical symptoms, occurs somewhat commonly in young girls, pregnant women, and patients with diabetes. This condition must be taken seriously because, if left untreated, it may result in pyelonephritis and, subsequently, permanent renal damage.

Casts

Casts are precipitated, cylindrical impressions of the nephrons. They comprise Tamm-Horsfall mucoprotein (uromucoid) from the tubular epithelia in the ascending limb of the loop of Henle. Casts form whenever there is sufficient renal stasis, increased urine salt or protein concentration, and decreased urine pH. In patients with severe renal disease, truly accurate classification of casts may require use of "cytospin" centrifugation and Papanicolaou staining for adequate differentiation. Unlike cells, casts should be examined under low power and are most often located around the edges of the coverslip.

Hyaline

The matrix of these casts is clear and gelatinous, without embedded cellular or particulate matter. They may be difficult to visualize unless a high-intensity lamp is used. Their presence indicates glomerular leakage of protein. This leakage may be temporary (as a result of fever, upright posture, dehydration, or emotional stress) or may be permanent. Their occasional presence is not considered pathologic.

Granular

These casts are descriptively classified as either coarse or finely granular. The type of embedded particulate matter is simply a matter of the amount of degeneration that the epithelial cell inclusions have undergone. Their occasional presence is not pathologic; however, large numbers may be found in chronic lead toxicity and pyelonephritis.

Cellular

Several different types of casts are included in this category. RBC or erythrocytic casts are always considered pathologic because they are diagnostic for glomerular inflammation that results in renal hematuria. They are seen in subacute bacterial endocarditis, kidney infarcts, collagen diseases, and acute glomerulonephritis. WBC or leukocytic casts are also always considered pathologic because they are diagnostic for inflammation of the nephrons. They are observed in pyelonephritis, nephrotic syndrome, and acute glomerulonephritis. In asymptomatic pyelonephritis, these casts may be the only clue to detection. Epithelial cell casts are sometimes formed by fusion of renal tubular epithelia after desquamation; occasional presence is normal. Many, however, are observed in severe desquamative processes and renal stases that occur in heavy metal poisoning, renal toxicity, eclampsia, nephrotic syndrome, and amyloidosis. Waxy casts are uniformly yellowish, refractile, and brittle appearing, with sharply defined, often broken edges. They are almost always pathologic because they indicate tubular inflammation or deterioration. They are formed by renal stasis in the collecting ducts and are, therefore, found in chronic renal diseases. Fatty casts are abnormal, coarse, granular casts with lipid inclusions that appear as refractile globules of different sizes. Broad (renal failure) casts may be up to two to six times wider than "regular" casts and may be cellular, waxy, or granular in composition. Like waxy casts, they are derived from the collecting ducts in severe renal stasis.

Crystals

Acid Environment

Crystals seen in urine with pH values of less than 7 include calcium oxalate, which are normal colorless octahedrons or "envelopes"; they may have an almost star-like appearance. Also seen are amorphous urates, normal yellow-red masses with a grain of sand appearance. Uric acid crystals found in this environment are normal yellow to red-brown crystals that appear in extremely irregular shapes, such as rosettes, prisms, or rhomboids. Cholesterol crystals in acid urine are clear, flat, rectangular plates with notched corners. They may be seen in nephrotic syndrome and in conditions producing chyluria and are always considered abnormal. Cystine crystals are also sometimes observed in acid urine; they are highly pathologic and appear as colorless, refractile, nearly flat hexagons, somewhat similar to uric acid. These are observed in homocystinuria (an aminoaciduria resulting in mental retardation) and cystinuria (an inherited defect of cystine reabsorption resulting in renal calculi).

Alkaline Environment

Crystals seen in urine with pH values greater than 7 include amorphous phosphates, which are normal crystals that appear as fine, colorless masses, resembling sand. Also seen are calcium carbonate crystals, which are

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normal forms that appear as small, colorless dumbbells or spheres. Triple phosphate crystals are also observed in alkaline urines; they are colorless prisms of three to six sides, resembling "coffin lids." Ammonium biurate crystals are normal forms occasionally found in this environment, appearing as spiny, yellow-brown spheres, or "thorn apples."

Other

Sulfonamide crystals are abnormal precipitates shaped like yellow-brown sheaves, clusters, or needles, formed in patients undergoing antimicrobial therapy with sulfa drugs. These drugs are seldom used today. Tyrosine/leucine crystals are abnormal types shaped like clusters of smooth, yellow needles or spheres. These are sometimes seen in patients with severe liver disease.[16]

PATHOPHYSIOLOGY

Glomerular Diseases

Disorders or diseases that directly damage the renal glomeruli may, at least initially, exhibit normal tubular function. With time, however, disease progression involves the renal tubules as well. The following syndromes have discrete symptoms that are recognizable by their patterns of clinical laboratory findings.

Acute Glomerulonephritis

Pathologic lesions in acute glomerulonephritis primarily involve the glomerulus. Histologic examination shows large, inflamed glomeruli with a decreased capillary lumen. Abnormal laboratory findings usually include rapid onset of hematuria and proteinuria (usually albumin and generally <3 g/d). The rapid development of a decreased GFR, anemia, elevated blood urea nitrogen (BUN) and serum creatinine, oliguria, sodium and water retention (with consequent hypertension and some localized edema), and, sometimes, congestive heart failure is typical. Numerous hyaline and granular casts are generally seen on UA. The actual RBC casts are regarded as highly suggestive of this syndrome. Acute glomerulonephritis is often related to recent infection by group A β-hemolytic streptococci. It is theorized that circulating immune complexes trigger a strong inflammatory response in the glomerular basement membrane, resulting in a direct injury to the glomerulus itself. Other possible causes include drug-related exposures, acute kidney infections due to other bacterial (and, possibly, viral) agents, and other systemic immune complex diseases, such as systemic lupus erythematosus and bacterial endocarditis.

Chronic Glomerulonephritis

Lengthy glomerular inflammation may lead to glomerular scarring and the eventual loss of functioning nephrons. This process often goes undetected for lengthy periods because only minor decreases in renal function occur at first and only slight proteinuria and hematuria are observed. Gradual development of uremia (or azotemia, excess nitrogen compounds in the blood) may be the first sign of this process.

Nephrotic Syndrome

Nephrotic syndrome (Fig. 27-6) can be caused by several different diseases that result in injury and increased permeability of the glomerular basement membrane. This defect almost always yields several abnormal findings, such as massive proteinuria (>3.5 g/d) and resultant hypoalbuminemia. The subsequent decreased plasma oncotic pressure causes a generalized edema as a result of the movement of body fluids out of vascular and into interstitial spaces. Other hallmarks of this syndrome are hyperlipidemia and lipiduria. Lipiduria takes the form of oval fat bodies in the urine. These bodies are degenerated renal tubular cells containing reabsorbed lipoproteins. Primary causes are associated directly with glomerular disease states.

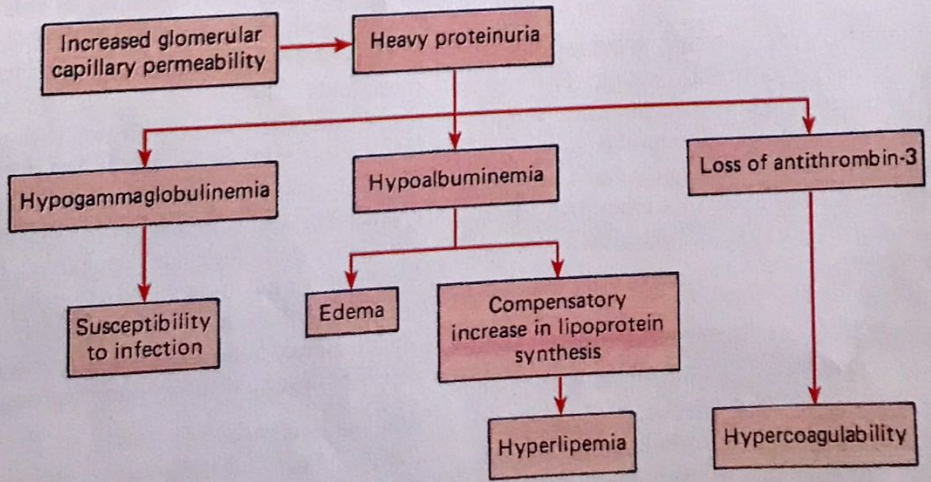

FIGURE 27-6 Pathophysiology of nephrotic syndrome.

Tubular Diseases

Tubular defects occur to a certain extent in the progression of all renal diseases as the GFR falls. In some instances, however, this aspect of the overall dysfunction becomes predominant. The result is decreased excretion/reabsorption of certain substances or reduced urinary concentrating capability. Clinically, the most important defect is RTA, the primary tubular disorder affecting acid–base balance. This disease can be classified into two types, depending on the nature of the tubular defect. In distal RTA, the renal tubules are unable to keep up the vital pH gradient between the blood and tubular fluid. In proximal RTA, there is decreased bicarbonate reabsorption, resulting in hyperchloremic acidosis. In general, reduced reabsorption in the proximal tubule is manifested by findings of abnormally low serum values for phosphorus and uric acid and by glucose and amino acids in the urine. In addition, there may be some proteinuria (usually <2 g/d).

Acute or chronic inflammation of the tubules and surrounding interstitium also may occur as a result of radiation toxicity, renal transplant rejection, viral–fungal–bacterial infections, and a reaction to medications. This is known as interstitial nephritis. Characteristic clinical findings in these cases are decreases in GFR, urinary concentrating ability, and metabolic acid excretion; leukocyte casts in the urine; and inappropriate control of sodium balance.[4,7]

Urinary Tract Infection/Obstruction

Infection

The site of infection may be either in the kidneys (pyelonephritis) or in the urinary bladder (cystitis). In general, a microbiologic colony count of more than 10^5 colonies/mL is considered diagnostic for infection in either locale. Bacteriuria (as evidenced by positive nitrite dipstick findings for some organisms), hematuria, and pyuria (leukocytes in the urine, as shown by positive leukocyte esterase dipstick) are all frequently encountered abnormal laboratory results in these cases. In particular, WBC (leukocyte) casts in the urine is considered diagnostic for pyelonephritis.[4,7,16]

Obstruction

Renal obstructions can cause disease in one of two ways. They may either gradually raise the intratubular pressure until nephrons necrose and chronic renal failure ensues or they may predispose the urinary tract to repeated infections.

Obstructions may be located in the upper or lower urinary tract. Blockages in the upper tract are characterized by a constricting lesion below a dilated collecting duct. Obstructions of the lower tract are evidenced by the residual urine in the bladder after cessation of micturition (urination); symptoms include slowness of voiding, both initially and throughout urination. Causes of obstructions can include neoplasms (e.g., prostate/bladder carcinoma or lymph node tumors constricting ureters), acquired diseases (e.g., urethral strictures or renal calculi), and congenital deformities of the lower urinary tract. The clinical symptoms of advancing obstructive disease include decreased urinary concentrating capability, diminished metabolic acid excretion, decreased GFR, and reduced renal blood flow. Laboratory tests useful in determining the nature of the blockage are UA, urine culture, BUN, serum creatinine, and CBC. Final diagnosis is usually made by radiologic imaging techniques.[5,8]

Renal Calculi

Renal calculi, or kidney stones, are formed by the combination of various crystallized substances, which are listed in Table 27-2. Of these, calcium oxalate stones are by far the most commonly encountered, particularly in the tropics and subtropics.

It is currently believed that recurrence of calculi in susceptible individuals is a result of several causes but mainly a reduced urine flow rate (related to a decreased fluid intake) and saturation of the urine with large amounts of essentially insoluble substances. Chemical analysis of stones is important in determining the cause of the condition. Specialized x-ray diffraction and infrared spectroscopy techniques are widely used for this purpose. Clinical symptoms are, of course, similar to those encountered in other obstructive processes: hematuria, urinary tract infections, and characteristic abdominal pain.[4,7,16]

TABLE 27-2 TYPES OF KIDNEY STONES

STONE COMPOSITION	CAUSE OF STONE FORMATION
Calcium oxalate	Hyperparathyroidism
	High urine calcium
	Vitamin D toxicity
	Sarcoidosis
	Osteoporosis
Magnesium ammonium phosphate	Infectious processes
Calcium phosphate	Excess alkali consumption
	Infection with urease-producing organisms
Uric acid	Gout
	High levels of uric acid in blood and urine
Cystine	Inherited cystinuria

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Renal Failure

Acute Kidney Injury

Acute kidney injury is a sudden, sharp decline in renal function as a result of an acute toxic or hypoxic insult to the kidneys. AKI is a common and serious condition that occurs in approximately 5% of all hospitalized patients. The risk, injury, failure, loss of function, end-stage renal disease (RIFLE) and the Acute Kidney Injury Network definitions of AKI are based on changes in both serum creatinine and urinary output; however, both display poor specificity and sensitivity for the early detection of AKI.[17,18] Novel urine and plasma biomarkers, such as NGAL and Kidney injury molecule-1 (KIM-1), are emerging as excellent biomarkers for the early prediction and prognosis of AKI. AKI is subdivided into three types, depending on the location of the precipitating defect.

Prerenal AKI: The defect lies in the blood supply before it reaches the kidney. Causes can include cardiovascular system failure and consequent hypovolemia.

Intrinsic AKI: The defect involves the kidney. The most common cause is acute tubular necrosis; other causes include vascular obstructions/inflammations and glomerulonephritis.

Postrenal AKI: The defect lies in the urinary tract after it exits the kidney. Generally, acute renal failure occurs as a consequence of lower urinary tract obstruction or rupture of the urinary bladder.

Toxic insults to the kidney that are severe enough to initiate acute renal failure include hemolytic transfusion reactions, myoglobinuria due to rhabdomyolysis, heavy metal/solvent poisonings, antifreeze ingestion, and analgesic and aminoglycoside toxicities. These conditions directly damage the renal tubules. Hypoxic insults include conditions that severely compromise renal blood flow, such as septic/hemorrhagic shock, burns, and cardiac failure. The most commonly observed symptoms of acute renal failure are oliguria and anuria (<400 mL/d). The diminished ability to excrete electrolytes and water results in a significant increase in extracellular fluid volume, leading to peripheral edema, hypertension, and congestive heart failure. Most prominent, however, is the onset of the uremic syndrome or kidney failure, in which increased BUN and serum creatinine values are observed along with the preceding symptoms. The outcome of this disease is either recovery or, in the case of irreversible renal damage, progression to chronic renal failure.[4,7]

CASE STUDY 27-1

A 52-year-old man with a history of AIDS, hypertension, diabetes mellitus, and alcohol abuse was found unconscious in his home by his roommate. In the emergency department, he was hypotensive (103/60 mm Hg), febrile (temperature 101°F), and unresponsive. Computed tomography scan of the abdomen showed cholecystitis and gallstones. Laboratory data are listed.

The patient was diagnosed with acute renal failure. He was administered intravenous fluids; BUN fell to 68 mg/dL and creatinine fell to 2.2 mg/dL. The patient's blood culture report was positive for *E. coli*. He was treated with tobramycin and cefepime. The patient continued to deteriorate and died 5 days after admission. Cause of death was multiorgan failure secondary to AIDS, sepsis, and alcoholic cirrhosis.

Questions

1. What is the significance of the patient's elevated CK? Explain why the physician ordered a CK-MB and troponin level. What can you conclude about the patient's cardiac status?
2. What is the cause of his acute renal failure?
3. What is the significance of the patient's large urine hemoglobin?
4. How would you interpret this patient's liver function tests considering his clinical history?

Drugs of Abuse	Negative	Urinalysis	
Serum ethanol	84 mg/dL	Hemoglobin	Positive
		WBC	4 HPF (0–4)
		RBC	2 HPF (0–4)
CK	3,308 U/L (24–204)	BUN	71 mg/dL (8–21)
CK-MB	15 ng/mL (0–7.5)	Creatinine	4.1 mg/dL (0.9–1.5)
Troponin T	<0.01 ng/mL (0–0.4)	Alkaline phosphatase	443 U/L (45–122)
pH	7.50	Aspartate aminotransferase	305 U/L (9–45)
pCO_2	27 mm Hg	Alanine aminotransferase	78 U/L (8–63)
Total CO_2	15 mmol/L	Gamma glutamyl transpeptidase	724 U/L (11–50)
		Total bilirubin	2.7 mg/dL (0.2–1.0)
		Direct bilirubin	2.4 mg/dL (0–0.2)

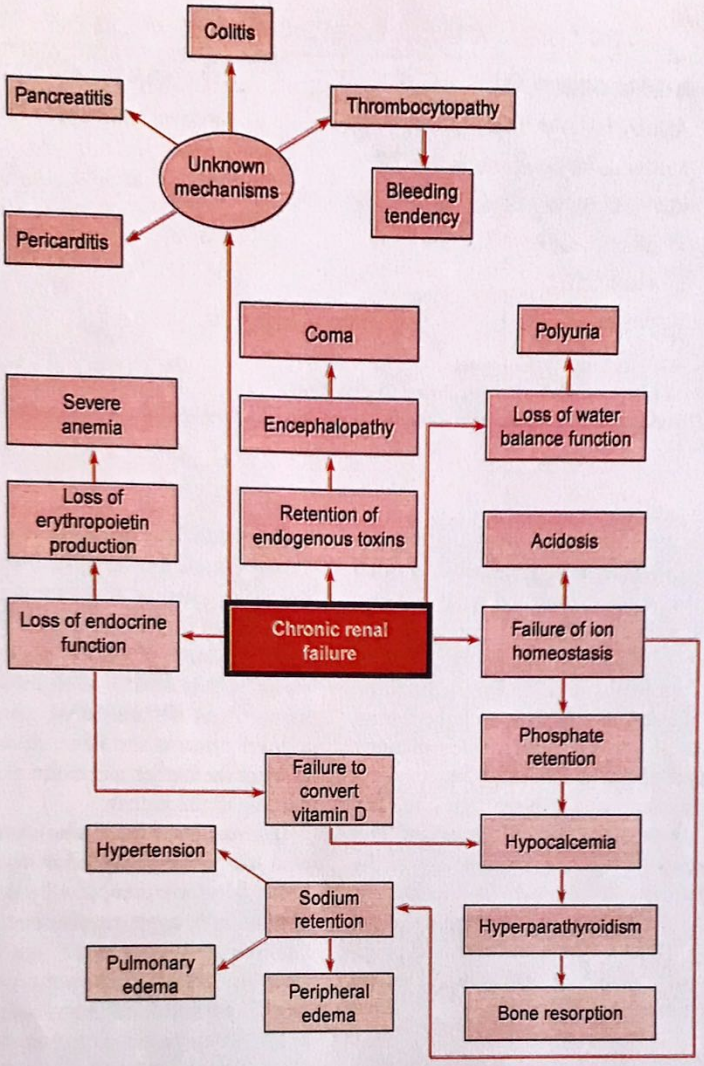

FIGURE 27-7 Pathophysiology of chronic kidney disease.

Chronic Kidney Disease

Chronic kidney disease is a clinical syndrome that occurs when there is a gradual decline in renal function over time (Fig. 27-7). According to the National Kidney Foundation, 1 in 11 U.S. adults has CKD and millions more are at risk (www.kidney.org). Early detection and treatment are needed to prevent progression to kidney failure and complications such as coronary vascular disease. The National Kidney Foundation has formulated guidelines for earlier diagnosis, treatment, and prevention of further disease progression. See Table 27-3 for the five stages of CKD. GFR and evidence of kidney damage based on measurement of proteinuria or other markers form the basis of the classifications.[19]

The conditions that can precipitate AKI also may lead to chronic renal failure. Several other causes for this syndrome are listed in Table 27-4.

Increasing Incidence of CKD

There is an increasing incidence of CKD in the United States due to the increase in diabetes, the aging population, obesity, and metabolic syndrome. Diabetes mellitus can have profound effects on the renal system. According to the National Kidney Foundation, diabetes is the leading cause of CKD and accounts for 45% of people diagnosed with kidney failure each year (www.kidney.org). The effects are primarily glomerular, but they may affect all kidney structures as well and are theorized to be caused by the abnormally hyperglycemic environment that constantly bathes the vascular system.[4,7]

Typically, diabetes affects the kidneys by causing them to become glucosuric, polyuric, and nocturic. These states are caused by the heavy demands made on the kidneys to diurese hyperosmotic urine. In addition, a mild proteinuria (microalbuminuria) often develops

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TABLE 27-3 SYSTEMATIC CLASSIFICATION OF CHRONIC KIDNEY DISEASE STAGES

STAGE	DESCRIPTION	GFR (ML/MIN PER 1.73 m^2)
	At increased risk[a]	≥60 (with risk factors)
1	Kidney damage with normal or ↑GFR	>90
2	Kidney damage with normal or ↓GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15

GFR, glomerular filtration rate; CKD, chronic kidney disease.

[a]At-risk patients should be screened. Stages 1–5 illustrate the progression of CKD.

Source: National Kidney Foundation. *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Executive Summary.* New York, NY: National Kidney Foundation, 2002:16.

between 10 and 15 years after the original diagnosis (see the section "Microalbumin"). Hypertension often manifests next, further exacerbating the renal damage. Eventually, chronic renal insufficiency or nephrotic syndrome may evolve, and each may be identified by their characteristic symptoms and laboratory findings. Early treatment of diabetes that focuses on tight control of blood glucose and prevention of high blood pressure may prolong the onset of chronic renal failure.

Aside from hypertension and diabetes, age is the key predictor of CDK. Due to the decline in fertility and increase in the average life span, the percentage of the population aged 65 years or older is projected to increase from 12.4% in 2000 to 19.6% in 2030, according to the U.S. Census Bureau. This continual rise, over the previous decade and those to come, contributes significantly to the increasing incidence of CKD.

TABLE 27-4 ETIOLOGY OF CHRONIC RENAL FAILURE

ETIOLOGY	EXAMPLES
Renal circulatory diseases	Renal vein thrombosis, malignant hypertension
Primary glomerular diseases	Systemic lupus erythematosus, chronic glomerulonephritis
Renal sequelae to metabolic disease	Gout, diabetes mellitus, amyloidosis
Inflammatory diseases	Tuberculosis, chronic pyelonephritis
Renal obstructions	Prostatic enlargement, calculi
Congenital renal deformity	Polycystic kidneys, renal hypoplasia
Miscellaneous conditions	Radiation nephritis

Epidemiologic evidence links obesity to CKD and kidney failure. However, diabetes mellitus and hypertension have potential confounding roles because obesity is a risk factor for diabetes and hypertension, the two most common causes of CKD and kidney failure. Recent studies show that obesity itself increases the risk of kidney injury.[20] As an individual gains weight, the nephron number remains the same; however, the GFR increases to meet the higher metabolic demands, which results in damage to the kidney.

The metabolic syndrome, characterized by the presence of at least three of the following risk factors—abdominal obesity, hypertension, low high-density lipoprotein cholesterol level, hypertriglyceridemia, or hyperglycemia—is a prevalent disorder in the United States. In a population study of a representative sample of the U.S. general population, the risk of CKD and microalbuminuria increased progressively with a greater number of components of metabolic syndrome.[21] Individuals with metabolic syndrome had a 2.6-fold increased risk of developing CKD compared with individuals without metabolic syndrome.[21] Interventions that target biochemical components of metabolic syndrome may reduce the risk of CDK.

Renal Hypertension

Renal disease–induced hypertension can be caused by decreased perfusion to all or part of the kidney (ischemia). Lack of perfusion may be caused by traumatic injury or narrowing of an artery or intrarenal arterioles. Chronic ischemia of any kind results in nephron dysfunction and eventual necrosis. The resulting changes in blood and body fluid volumes within the kidney trigger the activation of the renin–angiotensin–aldosterone system, setting off vasoconstriction that is manifested as persistent hypertension.

Renal hypertension can be evaluated by monitoring serum aldosterone, Na^+, and renin levels. As a result of the effect of aldosterone, there will be increased serum Na^+, decreased serum K^+, and increased urine K^+.

CASE STUDY 27-2

A 42-year-old man presented to the hospital admitting to have ingested 3 cups of antifreeze and a rodenticide product 10 hours prior. Upon arrival to the hospital, the patient was somnolent and afebrile and vitals were within normal limits. His chemistry results are shown below. Calcium oxalate crystals were found in his urine (pH 5). His urine toxicology screen was negative.

Na^+	139 mmol/L	Osmolality (serum)	416 mOsm/kg
K^+	4.3 mmol/L	Blood gases (arterial)	
Cl^-	94 mmol/L	pH	7.26
CO_2	10 mmol/L	pCO_2	13 mm Hg
BUN	9 mg/dL	pO_2	129 mm Hg
Creatinine	2.2 mg/dL	HCO_3^-	18 mmol/L
Glucose	167 mg/dL	Prothrombin time	12.8 s
Ca^{2+}	9.9 mg/dL	International normalized ratio	1.1
Albumin	4.5 g/dL		

Treatment with fomepizole (4-MP) was initiated to prevent further metabolism of ethylene glycol. The patient became agitated and was intubated for airway protection and placed on a propofol (sedative-hypnotic) drip. Nephrology was called and hemodialysis was started. Laboratory test results the morning after the first hemodialysis are listed below. The initial ethylene glycol level from time of presentation to the emergency room was received at this time and is included.

Na^+	143 mmol/L	Albumin	3.1 g/dL
K^+	4.1 mmol/L	Mg^{2+}	1.6 mg/dL
Cl^-	108 mmol/L	CK	405 U/L
CO_2	18 mmol/L	Osmolality	364 mOsm/kg
BUN	8 mg/dL	Blood gases (arterial)	
Creatinine	3.1 mg/dL	pH	7.4
Glucose	194 mg/dL	pCO_2	26 mm Hg
Ca^{2+}	7.7 mg/dL	pO_2	192 mm Hg
Ethylene glycol	499.4 mg/dL	HCO_3^-	15 mmol/L

The patient remained intubated and sedated. He continued to receive hemodialysis two times a day for 4 hours at a time. The patient also continued to receive fomepizole every 12 hours and following each round of hemodialysis. This treatment continued until the osmolar and anion gaps were normalized.

Questions

1. What caused the formation of the calcium oxalate crystals? What is the clinical significance of calcium oxalate crystal formation?
2. Calculate the anion and osmolar gaps for both sets of laboratory results. In this case, what is the cause of the anion and osmolar gaps? How are these values clinically significant?
3. What are other common drugs and toxins that can cause acute renal failure?

Therapy for AKI

Dialysis

In patients with AKI, uremic symptoms, uncontrolled hyperkalemia, and acidosis have traditionally been indications that the kidneys are unable to excrete the body's waste products and a substitute method in the form of dialysis was necessary. Dialysis is often instituted before this stage, however. Several forms of dialysis are available; however, they all use a semipermeable membrane surrounded by a dialysate bath.

In traditional hemodialysis (removal of waste from blood), the membrane is synthetic and outside the body. Arterial blood and dialysate are pumped at high rates (150 to 250 and 500 mL/min, respectively) in opposite directions. The blood is returned to the venous circulation and the dialysate discarded. The diffusion of low-molecular-weight solutes (<500 Da) into the dialysate is favored by this process, but mid-molecular-weight solutes (500 to 2,000 Da) are inadequately cleared. Creatinine clearance is about 150 to 160 mL/min.

In peritoneal dialysis, the peritoneal wall acts as the dialysate membrane and gravity is used to introduce and remove the dialysate. Two variations of this form are available, continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis; however, the process is continuous in both, being performed 24 hours a day, 7 days a week. This method is not as rigorous as the traditional method. Small solutes (e.g., potassium) have significantly lower clearance rates

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compared with the traditional method, but more large solutes are cleared and steady-state levels of blood analytes are maintained.

Continuous arteriovenous **hemofiltration** (ultrafiltration of blood), continuous venovenous hemofiltration, continuous arteriovenous hemodialysis, and continuous venovenous hemodialysis together make up the slow continuous renal replacement therapies developed to treat acute renal failure in critically ill patients in intensive care settings. In these methods, the semipermeable membrane is again outside the body. Solutes up to 5,000 Da (the pore size of the membranes) and water are slowly (10 mL/min) and continuously filtered from the blood in the first two methods, causing minimal changes in plasma osmolality. Volume loss can be replaced in the form of parenteral nutrition and intravenous medications. The final two methods are similar to the filtration methods, but a continuous trickle of dialysis fluid is pumped past the dialysis membrane, resulting in continuous diffusion and a doubling of the urea clearance.

Therapy for Kidney Failure

For patients with irreversible renal failure, dialysis and transplantation are the only two therapeutic options. Initiation of either treatment occurs when the GFR falls to 5 mL/min (10 to 15 mL/min in patients with diabetic nephropathy).

Dialysis

Traditional hemodialysis or its more recent, high-efficiency form and peritoneal dialysis are the available methods. The clinical laboratory used in conjunction with a hemodialysis facility must be able to adequately monitor procedural efficiency in a wide variety of areas. Renal dialysis has basic goals, and specific laboratory tests should be performed to evaluate the achievement of each goal.

Transplantation

The most efficient hemodialysis techniques provide only 10% to 12% of the small solute removal of two normal kidneys and considerably less removal of larger solutes. Even patients who are well dialyzed have physical disabilities and decreased quality of life. Kidney transplantation offers the greatest chance for full return to a healthy, productive life. However, this option is limited by the significant shortage of donor organs. For kidney failure patients, waiting for an organ donation can vary from several months to several years.

Renal transplantation is from a compatible donor to a recipient suffering from irreversible renal failure. The organ can be from a cadaver or a live individual (80% and 20%, respectively, of all kidney transplants in the United States). For this procedure to be successful, the body's immune response to the transplanted organ must be suppressed. Therefore, the donor and recipient are carefully

CASE STUDY 27-3

A 78-year-old woman with a history of hypertension, aortic thoracic graft, and esophageal reflux disease complained of fever (100°F) and weakness. She had been treated 3 weeks before at the hospital for a urinary tract infection. She was admitted to the hospital for a diagnostic workup and transfusion. Her laboratory results are as follows:

Na^+	129 mmol/L	Hct	25.6%
K^+	3.7 mmol/L	Hgb	8.5 g/dL
Cl^-	97 mmol/L	WBC	9,700
CO_2	19 mmol/L		
BUN	52 mg/dL		
Creatinine	3.2 mg/dL		

Urine culture was positive for *Citrobacter*. Urinalysis results are listed:

Color	Hazy/yellow
Specific gravity	1.015
pH	5
Blood	Large
Protein	2
Glucose	Negative
Ketones	Negative
Nitrates	Negative
RBC	>25
WBC	1–4
Casts	Granular, 1–4

The patient's renal function continued to decline, and she was put on hemodialysis. A renal biopsy was performed that showed end-stage crescentic glomerulonephritis. Two days later, the patient sustained a perforated duodenal ulcer, which required surgery and blood transfusion. Subsequently, she developed coagulopathy and liver failure. Her condition continued to deteriorate in the next few days, and she died following removal of life support.

Questions

1. Looking at the urinalysis, what is the significance of the results of 2+ protein and >25 RBCs?
2. What is the most likely cause of glomerulonephritis?
3. Why was the patient put on hemodialysis?

screened for ABO blood group, human leukocyte antigen (HLA) compatibility, and preformed HLA antibodies. The HLA system is the major inhibitor to transplantation.

Although kidney transplants have the capacity to function for decades, the mean half-life of a cadaveric transplant is approximately 7 years. The mortality rate is not significantly different from hemodialysis. Three-year graft survival figures vary from 65% to 85%, with live grafts doing better. It has been reported that there is no difference in patient survival among hemodialysis, CAPD, and cadaveric kidney transplantation. Live related-donor transplantation is associated with a better patient survival than other therapeutic options for kidney failure.

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QUESTIONS

1. Calculate creatinine clearance, given the following information: serum creatinine, 1.2 mg/dL; urine creatinine, 120 mg/dL; urine volume, 1750 mL/24 h; body surface area, 1.80 m^2.

2. Predict GFR in a 50-year-old woman who weighs 60 kg using the Cockcroft-Gault equation. Her serum creatinine level is 2.5 mg/dL.

3. The measurement of serum cystatin C, a small protein produced by nucleated cells, is useful for
   a. Detecting an early decrease in kidney function
   b. Calculating creatinine clearance
   c. Diagnosing end-stage renal disease
   d. Monitoring dialysis patients

4. Acute renal failure can be classified into three types. List each type and give an example of each.
   a. _____
   b. _____
   c. _____

5. The proximal tubule functions to
   a. reabsorb 75% of salt and water.
   b. concentrate salts.
   c. form the renal threshold.
   d. reabsorb urea.

6. Renal clearance is the
   a. volume of plasma from which a substance is removed per unit of time.
   b. volume of urine produced per day.
   c. amount of creatinine in urine.
   d. urine concentration of a substance divided by the urine volume per unit of time.

7. Renin release by the kidney is stimulated by
   a. a decrease in extracellular fluid volume or pressure.
   b. increased plasma sodium concentration.
   c. increased dietary sodium.
   d. renal tubular reabsorption.

8. The set of results that most accurately reflects severe renal disease is
   a. *serum creatinine*, 3.7 mg/dL; *creatinine clearance*, 44 mL/min; *BUN*, 88 mg/dL
   b. *serum creatinine*, 1.0 mg/dL; *creatinine clearance*, 110 mL/min; *BUN*, 17 mg/dL
   c. *serum creatinine*, 2.0 mg/dL; *creatinine clearance*, 120 mL/min; *BUN*, 14 mg/dL
   d. *serum creatinine*, 1.0 mg/dL; *creatinine clearance*, 95 mL/min; *BUN*, 43 mg/dL

9. Creatinine clearance results are corrected using a patient's body surface area to account for differences in
   a. muscle mass.
   b. age.
   c. dietary intake.
   d. sex.

10. A patient is suffering from an acute bleed. What is the most accurate way to describe the subsequent acute kidney injury?
    a. Prerenal acute kidney injury
    b. Renal acute kidney injury
    c. Postrenal acute kidney injury
    d. None of the above apply

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